Jens-Peter Gregersen

Research and Development of Vaccines and Pharmaceuticals from Biotechnology

A Guide to Effective Project Management, Patenting and Product Registration

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Distribution:
VCH, P. O. Box 101161, D-69451 Weinheim, Federal Republic of Germany
Switzerland: VCH, P. O. Box, CH-4020 Basel, Switzerland
United Kingdom and Ireland: VCH, 8 Wellington Court, Cambridge CB1 1HZ, United Kingdom
USA and Canada: VCH, 220 East 23rd Street, New York, NY 10010–4606, USA
Japan: VCH, Eikow Building, 10-9 Hongo 1-chome, Bunkyo-ku, Tokyo 113, Japan

ISBN 3-527-30059-7

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D-65926 Frankfurt/M.

Published jointly by
VCH Verlagsgesellschaft mbH, Weinheim (Federal Republic of Germany)
VCH Publishers Inc., New York, NY (USA)

Editorial Director: Dr. Hans-Joachim Kraus
Production Manager: Dipl.-Wirt.-Ing. (FH) H.-J. Schmitt

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data:
A catalogue record for this book
is available from the British Library

Die Deutsche Bibliothek – CIP-Einheitsaufnahme:
Gregersen, Jens-Peter:
Research and development of vaccines and pharmaceuticals
from biotechnology : a guide to effective project management,
patenting and product registration / Jens-Peter Gregersen. – Weinheim ;
New York ; Basel ; Cambridge ; Tokyo : VCH, 1994
ISBN 3-527-30059-7

Printing: Strauss Offsetdruck, D-69509 Mörlenbach
Bookbinding: Großbuchbinderei J. Schäffer, D-67269 Grünstadt
Printed in the Federal Republic of Germany.

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Preface

This book has been written for researchers in academic laboratories and industry, who are currently experiencing exciting scientific changes in the traditionally empiric life sciences, which coincide with a growing economic awareness in these areas. The biomedicinal sciences are particularly affected by an increasing dicotomy between highly innovative research and – due to regulatory limitations – very conservative development of pharmaceutical products. Scientists who are engaged in applied research or development, spanning the widening gap between fundamental research and its application, have to cope with increasing scientific and regulatory demands. Rising concerns about the cost of research and development, time performance and competitiveness cause additional distress.

Conventional biological products were mostly developed by very small, highly interactive groups. The basic methodological repertoire was limited and most of it was shared by researchers, developers and manufacturers. This situation is near optimal for the development of new products. It is fast and effective and is affordable for small companies which operate on a national basis, but it no longer applies to modern biotechnological products.

Biological products and particularly vaccines always had a special position among medicinal products and enjoyed several regulatory privileges. Modern biological products deviate from the traditional ones by more defined active ingredients, more complex formulations and by their manufacturing and analytical methods. Vaccines of the future will be applied for purposes other than the prevention of infections and will probably even differ by their mode of action, e.g. by the direct application of DNA. These new products have more and more in common with chemical pharmaceutical products. Thus pharmacokinetic, pharmacodynamic, safety and analytical investigations rank much higher and many more specialists are required to develop these products.

As a consequence, modern biological pharmaceuticals are no longer developed on the fast track. Their development times are much longer, the costs will be similar to those of drugs and they will have to recoup the investment into research and development on larger, international markets. The technical, regulatory and commercial basis for biomedicinal products has changed and with it the underlying research activities. Scientists in biomedicinal research should be aware of the changed situation and its impact on their activities.

This book is an attempt to summarize information on the fundamentals of pharmaceutical product development for modern biomedicinal products and to combine these with specific recommendations for effective planning and management of applied research and development projects. A reasonable selection of information was necessary to avoid confusions by too many details. This inevitably leads to omissions and simplifications, particularly on patent and registration issues. The reader should bear in mind that these sections are primarily intended to

explain the fundamental rules. For specific advice and interpretation of special cases the original and official documents should be consulted.

Acknowledgements
I gratefully acknowledge the efforts of several colleagues at Biotech Australia Pty. Ltd. and Hoechst AG who contributed greatly to this work. Gary Cobon critically reviewed the manuscript and made many important suggestions for its improvement. Richard Brown, Gerard Henry, Katrine Hill, Jim Hungerford, Rosalind Kaldor, Peter Kennedy, Jürgen Lindner and Werner Schmidt corrected and improved several major sections. Catherine Nelson-Smith and Sheila Yong provided valuable ongoing library and information support, Stephen Harston generously provided information material on regulatory aspects and Beverly Smallbone and Anne Marshall helped in typing the manuscript.
I also wish to thank all those colleagues at Behringwerke AG, Hoechst AG and subsidiaries and Biotech Australia Pty. Ltd. who contributed directly or indirectly, voluntarily or unwittingly to this book by providing competent advice and by setting countless good examples of achievements by cooperation and putting effective management into practice, without neglecting human interrelationships. The views expressed in this book are those of the author and are not necessarily those of the persons and companies mentioned in the acknowledgements.

Frankfurt, March 1994 Jens-Peter Gregersen

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'Would you tell me, please, which way I ought to go from here?'

'That depends a good deal on where you want to get to.'

'I don't much care where.'

'Then it doesn't matter which way you go.'

(Lewis Carrol: Alice's adventures in wonderland)

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Biotechnology in Pharmaceutical Research

Recombinant DNA techniques have opened up almost unlimited possibilities to generate biological molecules for vaccines and therapeutics for the prevention, diagnosis and therapy of diseases in man and animals. Twice in history similar breakthroughs were achieved: The introduction of pure bacterial cultures and of cell culture techniques to produce viruses were technical innovations, which each resulted in a series of new and extremely beneficial vaccines. Compared to recombinant DNA techniques, those historical achievements may only be minor steps forward in a limited area. We now hold a universal key to all proteins and antigens in our hands and with it the possibilities to develop not only new vaccines but also a variety of new therapeutics.

The ability to make defined peptides, proteins and antigens is only one aspect of the new technology. Other, more basic aspects may be even more exciting. The new tools and methods have stimulated basic research across all life sciences and the knowledge about basic physiological and biological processes has increased tremendously. Traditional applied sciences, such as immunology, virology, bacteriology and parasitology, have gained access to knowledge and methods to study the fundamental mechanisms which control the subject of these sciences and have moved into new and exciting basic research areas. With every newly discovered molecule and mechanism, new possibilities have arisen to apply the discoveries for medicinal purposes. Research funds and investment soared - and with these the revenue expectations.

The technology to apply the new knowledge was unable to keep pace with the speed of this scientific progress, which resulted in a widening gap between basic research and applied research. The legal and regulatory authorities which control the applications were even less prepared and are still struggling to cope with the new situation.

The development of technological innovations is following scientific progress with some delay and at a much slower pace. The time that it takes to develop new products is almost invariably underrated. On average it took about 20 years from conception to realization of major innovations (Batelle, 1973; Rosen, 1976). This average figure was deduced from the development periods of a whole range of innovative products, including for example antibiotics (30 years), instant coffee (22 years), liqid shampoo (8 years) and the zipper (30 years).

Can we expect that biomedicinal product concepts will be developed much faster?

Biotechnology in the 1990's

After more than a decade of modern molecular biology research, it appears appropriate to take stock of the assets and deficiencies of the new technology and to adjust the future direction if necessary. An evaluation such as this must concentrate on the situation in the USA, which has been at the forefront of development.

On average, each of the 550 pure biotechnology firms in the USA went into the 1990's with a turnover of $ 11 million and a research and development budget of $ 4.6 million (North Carolina Biotechnology Center companies database; see also Dibner, 1989). Only 30% of the income of these companies was derived from product sales (Stone, 1993). Most of this income was generated by only a few of the 550 firms, the vast majority had no significant sales at all. In these companies research and development activities account for considerable losses, which cannot be maintained over a very long period of time. One would expect a whole flood of new, profitable products from these companies within the following few years. But if we look for products from biotechnology on the current market, there is still only a handful of pharmaceutical products and some diagnostic tests. The list of products in the advanced clinical development is also not very impressive. Most product candidates in clinical development are still in Phase I clinical trials (see for example Pharmaceutical Manufacturers Association survey reports and Vitetta et al., 1993). Experience tells us that many of these developments will be abandoned. Successful products in Phase I usually still need about 3 years or more to get onto the market. Quite obviously most of the expected biomedicinal development products have not advanced as expected.

An evaluation of the situation of US biotechnology by an insider (Dibner, 1989) may be helpful to explain the reasons. According to his assessment, successful basic research and favourable environmental factors, such as a strong pharmaceutical industry, entrepreneurial spirit and a culture which supports innovation and risk taking characterize the strengths of US biotechnology. Contrary to these advantages, Dibner noticed several significant weaknesses which may be summarized under three headings:

- Technical weaknesses, e.g. in fermentation and bioprocess engineering;
- Structural weaknesses, e.g. in applied research and training programs, lack of collaboration and targeted programs, short-term funding, small firms;
- Regulatory uncertainties concerning patenting, medicines registration and other legal aspects.

Uncertainties about regulations for a new technology are not unusual. Regulatory systems are established in parallel with the applications of new technologies. The details cannot be determined before the subject of these regulations is defined. Thus, patenting and registration policies for products from biotechnology are still developing and will continue to do so for several more years. Two separate chapters below will deal with these aspects in detail.

The noted technical weaknesses are certainly not due to the total neglect of such issues and are probably not unexpected. It simply takes considerable time and effort to develop the technology to exploit the new techniques. Those who started early, developing the techniques to a level where these can be sufficiently controlled for an industrial application, are more likely to win the race to the market place. In the case of medicinal products from biotechnology, fermentation technology is an essential element of the technical development. In Japan this has been recognized very early and Japan's breweries have put considerable money into fermentation research.

In principle, the technical problems can be solved if sufficient time and money is available. But the results will not always be as desired, and it will initially be necessary to accept many compromises in terms of scale, yields, reproducibility and cost of production. Given the technical feasibility, the impact of time, money and lower than expected performance tend to be neglected. In the end they may be critical success factors!

Structural problems can have significant inhibitory effects and are probably the most difficult ones to change. A central problem lies in the observation that target orientation and collaboration is lacking. In the context of biomedicinal research and development, insufficient information about the magnitude of the task and overrated capabilities are partly responsible for these shortcomings, but the true reasons lie deep in our research system and warrant further consideration.

Research Structures

If one considers the structures of biomedicinal research, its purpose must be defined first. Medicinal research is done (and funded by governments) to generate new knowledge and in order to promote public and economic welfare. Research must not stop after the knowledge has been published. Science fulfils its purpose only, if it enables the public to apply the knowledge and to benefit from it. Medicinal research must lead to applications of scientific discoveries for the prevention and therapy of diseases.

Our current publication-driven research system motivates those who discover and publish. Those who build on these foundations, find all the missing parts, set